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CASE REPORT

Three case reports of involuntary muscular movements as adverse reactions to sacubitril/valsartan

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Entresto® is a fixed dose association of sacubitril (an inhibitor of neprilysin or neutral endopeptidase) and valsartan [1]. The pivotal trial showed significant and relevant clinical benefit on cardiovascular death and hospitalizations for heart failure compared to enalapril [2]. Usual adverse reactions include symptomatic hypotension and renal impairment. We report three cases of abnormal muscular movements, starting shortly after sacubitril/valsartan initiation and resolving shortly after treatment withdrawal. Although considered non-serious by the physician, these effects affected the patients' quality of life necessitating drug withdrawal.

All patients were men, aged 65 to 79 years old, with low ejection fraction (25% to 30%) heart failure and followed in the Cardiology Department of Tours University Hospital. Despite optimal treatment including beta-blockers and renin-angiotensin-aldosterone system antagonists (Table 1), they were re-admitted for decompensated heart failure. Sacubitril/valsartan was initiated at a normal (49/51 mg BID) or reduced (24/26 mg BID) starting dose. Shortly after drug initiation (12 h to 4 days) patients complained of non-painful, involuntary, abnormal and sporadic limbs and head movements. In patient 1, involuntary movements developed after hospital discharge, persisted for several weeks and led to a neurological workup. Cerebral tomodensitometry showed no recent ischemic images (image of ischemic sequelae) with. Electroencephalogram showed normal basal rhythm with intermittent myoclonic head and arms movements. Sacubitril/valsartan was eventually discontinued 4 months after drug initiation, and involuntary movements disappeared within 48 h. For the other two patients, similar symptoms developed during hospitalization, 12 h after drug initiation. Sacubitril/valsartan was suspected since it was the only drug modification before symptoms onset. Because of the incapacitating nature of the symptoms sacubitril/valsartan was rapidly discontinued and symptoms disappeared shortly (24 to 48 h) after drug withdrawal. All patients remained symptom free for the next months, with no drug re-challenge. Of notice, out of involuntary movements episodes, neurological examinations were unremarkable in all patients and their cardiovascular status was stabilized at the time of symptoms onset. The three patients died of heart failure within the year following these episodes.

To our knowledge, this is the first report of involuntary muscular movements considered to be related to sacubitril/valsartan. There was a reasonable time relationship between drug intake and symptoms onset (peak plasma concentrations of 2 h for LBQ657, sacubitril active metabolite) and between drug withdrawal and symptoms disappearance (half-life of 10 h for valsartan and 12 h for LBQ657), which make the causality possible [3, 4]. Drug–drug interaction between sacubitril/valsartan and statins was considered possible in patient 1 (atorvastatin), but unlikely in patient 2

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Table 1

Main characteristics of the three patients and of the adverse event

	Patient 1	Patient 2	Patient 3
Gender, age	Male, 79 years	Male, 65 years	Male, 71 years
Weight	84 kg	83 kg	94 kg
Heart disease	Ischaemic, LVEF 30%AF, AVNA, CRTmoderate to severe MR	Dilated/ischaemic, LVEF 30%ICD + CRT, AF	dilated, LVEF 35%AF, AVNA, ICD + CRTsevere MR, moderate AR
Comorbidities	History of stroke, peripheral vascular disease	Peripheral vascular disease, chronic kidney disease (GFR 32 ml/min/1.73 m^2), gouty rheumatism	Peripheral vascular disease, chronic kidney disease (GFR 28 ml/min/1.73 m^2)
Risk factors	Hypertension, hypercholesterolaemia, smoking, heredity	Hypertension, diabetes, heredity	Hypertension
Concomitant treatments	Dabigatran, bisoprolol, ramipril (stopped), eplerenone, furosemide, amlodipine, atorvastatin, nicorandil	Fluindione, bisoprolol, trandolapril (stopped), spironolactone, furosemide, pravastatin, repaglinide	Fluindione, nebivolol, perindopril (stopped), spironolactone, furosemide, amiodarone
Sacubitril/valsartan			
Starting dose (mg)	49/51 increased to 97/103	49/51	24/26
Duration	4 1/2 months	4 days	1 day
AE onset (days)	4 days	12 h	12 h
DCA/DCO	Drug withdrawn/reaction abated within 24 h	Drug withdrawn/reaction abated within 24 h	Drug withdrawn/reaction abated within 24 h
RCA/RCO	No/–	No/–	No/–
Neurological workup	Cerebral TDM, EEG	No	No

AF: atrial fibrillation; AR: aortic regurgitation; AVNA: atrioventricular node ablation CRT: cardiac resynchronization therapy; DCA/DCO: dechallenge action/dechallenge outcome; EEG: electroencephalogramme; GFR: glomerular filtration rate; ICD: implantable chest defibrillator; LVEF: left-ventricular ejection fraction; MR: mitral regurgitation; RCA/RCO: rechallenge action/rechallenge outcome; TDM: tomodensitometry.

(pravastatin) and patient 3 (no statin); drug–drug interactions with other concomitant medications were considered unlikely [5, 6].

Since we found no published reports of similar adverse reactions, we searched VigiBase®, the WHO international database of suspected adverse drug reactions (ADRs). VigiBase® included more than 14 million Individual Case Safety Reports in January 2017, with data being collected from more than 100 countries. These data come from a variety of sources, and the likelihood of a causal relationship is not the same in all reports; therefore, interpretations of ADRs may be misleading. For ADRs reported with sacubitril/valsartan (coded according to the WHODrug™ dictionary), we used the following Medical Dictionary for Regulatory Activities (MedDra, 19.1 version) preferred terms (PTs) 'Muscle spasm', 'Muscle twitching', 'Myofascial spasm', 'Dyskinesia', 'Clonus', 'Myoclonus', 'Dystonia' and High Level Group Terms (HLGT) 'Neuromuscular disorders'. We retrieved 40 unique case reports, excluding ours, from which 31 cases of 'muscle spasms' were reported mainly by patients (22 cases, 71%). Sacubitril/valsartan was the only suspected drug in 26 cases, 17 (65%) reported by patients. Only 4/26 cases were considered serious (15%). In five cases, muscle spasms or twitches were the only symptoms reported mainly by patients (four cases). Because it caused/prolonged hospitalization, the fifth case was considered serious by the reporting physician. Similarly to our three case reports, sacubitril/valsartan was withdrawn after 4 days leading to recovery in this patient. Other involuntary movements were also reported, and summary of these adverse reactions with sacubitril/valsartan may be accessed at http://www.vigiaccess.org/.

We have no clear pharmacological explanation for these adverse reactions. Sacubitril/valsartan central nervous system safety was assessed in preclinical pharmacology studies [7, 8]. In repeated dose studies in mice and rats, but not in primates, increased locomotor activity, twitches and sensitivity to touch were observed with sacubitril/valsartan [7]. These effects occurred at exposure levels below the clinical target exposure [8]. However, given the sporadic nature of these findings, they were not deemed to be of toxicological significance [7]. No general nor neurobehavioral effects of sacubitril were observed in male mice at a single dose [7]. Finally, enkephalinase inhibitors, neutral endopeptidase inhibitors being part of this family, were previously shown to interfere with the dopaminergic system in experimental models [9].

Further studies investigating potential mechanisms of these adverse reactions are necessary. Caregivers should be aware of these potential adverse reactions of sacubitril/valsartan, mostly non-severe and reported by patients. They should also report and encourage reporting of such adverse reactions by patients [10], especially when they impact quality of life. Given the important clinical benefit of sacubitril/valsartan, the risks and benefit of withdrawal should be carefully considered if symptoms are incapacitating.

Competing Interests

T.B.-A., T.G. and L.V. have nothing to disclose. D.A. reports personal fees and non-financial support from Astra-Zeneca, personal fees from Novartis, grants and personal fees from Lilly, personal fees and non-financial support from MSD, personal fees from Servier, personal fees from Amgen, personal fees from Bayer, personal fees from Sanofi, personal fees from Daiichi-Sankyo and personal fees from BMS, all outside the submitted work. L.F. has been consultant for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novartis and Sanofi Aventis and has been on the speakers bureau for Bayer, BMS, Pfizer, Boehringer Ingelheim, Daiichi Sankyo and Medtronic.

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Ethics committee approval and subjects' consents were not sought, since the three patients were followed up in clinical practice in our department, data for publication were retrospectively retrieved and all three patients were deceased before the preparation and submission of the manuscript.

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